receptors.[9] The present data show that these AMPA-mediated responses are inhibited by the activation of the mesocortical DA system. Such a depression of glutamatergic transmission by DA has been previously observed in PFC slices where monosynaptic EPSPs mediated through AMPA receptors were reduced during superfusion of DA.[7] Interestingly, DA also modulates long term changes in synaptic efficacy in PFC slices, as DA applied during tetanization of superficial layers prevents the induction of long term potentiation and unmasks long term depression in layer V pyramidal cells.[20] Long term potentiation is observed in the PFC following high frequency stimulation of the hippocampus, and this effect involves NMDA receptors.[21,22] It will therefore be of interest to examine the effects of DA application or VTA stimulation on these long term changes in synaptic efficacy of the hippocampo-PFC pathway.

In the present study, we have also shown that PFC neurones which receive an excitatory input from the hippocampus can be antidromically driven from the NAcc and/or the VTA. Thus, the NAcc and the VTA are probably targets of PFC neurones excited by the hippocampal stimulation. These data agree with anatomical studies which have described projections from the prelimbic and medial orbital areas of the PFC to the NAcc (mainly the core subdivision)[11] and the VTA.[23] There is also evidence that PFC terminals form asymmetrical synapses on spiny neurones in the NAcc and on DA neurones in the VTA.[24] Altogether these results support the existence of hippocampo-PFC-NAcc and hippocampo-PFC-VTA circuits. Thus, in addition to its known direct influence on the NAcc,[12] the hippocampus could also indirectly modulate the NAcc through the PFC. However, these direct and indirect hippocampal inputs mainly occur on different subterritories of the NAcc, the shell and the core respectively. The existence of an hippocampo-PFC-VTA circuit suggests that the hippocampus may indirectly control DA neurones in the VTA through the PFC. It is well established that DA neurones in the VTA which innervate the NAcc play a critical role in the sensitization process induced by repeated administration of drugs of abuse,[25] and lesions of the fimbria prevent this sensitization.[26] It is tempting to propose that the hippocampus could play a role in regulating the development of drug sensitization not only through its direct connection to the NAcc but also through the hippocampo-PFC-VTA circuit.

Conclusion

Our results indicate that the mesocortical DA system exerts an inhibitory influence on excitatory responses induced in PFC neurones by hippocampal stimulation and suggest that, through the PFC, the hippocampus could indirectly control the activity of NAcc and VTA neurones. The PFC has often been suggested as a locus of dysfunction in schizophrenia and DA systems have been implicated in this mental disorder. Changes in the nature of signals passing through the hippocampo-PFC-NAcc or the hippocampo-PFC-VTA circuits resulting from a dysfunction of the mesocortical DA system could contribute to some of the characteristic disorders observed in schizophrenia.

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Galanin inhibits the vasodilatatory basalocortical cholinergic system in the anaesthetized rat

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In order to test the putative interaction between galanin and the vasodilatatory basalocortical cholinergic system, anaesthetized ventilated rats received a microinjection into the substantia innominata of 0.9% NaCl, 50 nmol carbachol, 50 nmol carbachol and 200 ng galanin, or 200 ng galanin. Cerebral blood flow (CBF) was measured with [^{14}C]iodoantipyrine by the tissue sampling technique immediately following the intracerebral infusions. Under coinjection conditions, the flow increases observed after carbachol microinjection in the ipsilateral temporal and frontoparietal cortices were found to be significantly reduced (−37%, $p \leq 0.02$ and −25%, $p \leq 0.05$ respectively) compared with carbachol stimulated rats. The infusion of galanin by itself had no effect on CBF. These results demonstrate that galanin inhibits the vasodilatatory basalocortical cholinergic system and thus may possibly influence CBF by indirect mechanisms.

Key words: Galanin; Cholinergic; Carbachol; Substantia innominata; Cerebral blood flow; Rat

Introduction

The ascending cholinergic system from the substantia innominata (SI), the rodent equivalent of the nucleus basalis of Meynert (NBM) in primates, to the neocortex is involved in the modulation of cerebral blood flow (CBF). Indeed, electrical stimulation of the SI induces vasodilatation, mediated by muscarinic and nicotinic receptors, in the ipsilateral neocortex.[1–3] In a comparable manner, increases in hippocampal CBF are elicited by medial septal stimulation.[4] As electrical stimulation may activate neuronal somata and 'fibres de passage', we have previously investigated[5] a neurochemical stimulation of the SI using local microinjection of carbachol. Infusion of this cholinergic agonist induces significant increases in CBF in the ipsilateral neocortex and thus may represent a model better adapted (than that of electrical stimulation) for the further investigation on the refined pharmacology of the basolocortical cholinergic system.

The basalocortical cholinergic system is itself modulated by other neurotransmitters such as somatostatin[6] or GABA.[7,8] Another neuromodulator that appears to be able to interact with the cholinergic baslocortical system is represented by galanin, a 29 amino acid peptide. Indeed, galanin has been previously demonstrated to exert an inhibitory modulatory action on cholinergic systems *in vitro*[9,10] as well as on cholinergically linked learning and memory processes.[11] Since galanin and acetylcholine (ACh) are both present within the SI/NBM,[12] the aim of this study was to define the possible functional involvement of galanin on the cholinergic somata of the SI; an interaction which has been previously described for the septo-hippocampal cholinergic pathway.[9,10] Explicitly, we have investigated a galaninergic modulation of the cholinergic basalocortical influences on CBF.

Materials and Methods

Animals: Experiments were performed on male Sprague Dawley rats (264 ± 3 g, mean ± s.e.m.; IFFA Credo, France), maintained on a standard 12 h/12 h light-dark cycle and allowed food and water *ad lib*.

Surgery: Animals were anaesthetized with α-chloralose (50 mg kg^{-1}, s.c.) and urethane (500 mg kg^{-1}, i.p.) following induction with halothane (4.5% then 1% in O_2). Catheters were placed in each femoral artery and vein and the trachea was cannulated. The skin incisions were infiltrated with xylocaine and were carefully sutured. The rats were ventilated artificially (Harvard Apparatus, Model 683) and were transferred into a stereotaxic frame. Continuous monitoring of arterial pressure and heart rate was recorded through one of the femoral catheters connected to a pression transducer and amplifier (Gould, Model 1170). After craniotomy, a stainless steel cannula (200 μm outer diameter) was inserted into the right SI (interaural axis +7.2, lateral +2.9 and vertical −8.2 from the surface of the calvarium[13]). Following completion of the surgical procedures, halothane was discontinued.

Blood was periodically sampled for measurement of p_aCO_2, p_aO_2 and pH_a (Radiometer ABL 300); tidal volume was adjusted in order to maintain physiological values of $p_aCO_2 \sim 35$ mmHg, $p_aO_2 > 150$ mmHg and $pH_a \sim 7.4$. Rectal temperature was maintained constant by means of a thermoregulated blanket.

Microinjections: The cannula was connected to a microinfusion pump (Carnegie Medicin, CMA/100). Each animal received a microinjection of 100 nl over a period of 10 min of 0.9% NaCl solution ($n = 8$; sham group), 50 nmol of carbamylcholine chloride ($n = 8$; carbachol group), a mixture of 50 nmol of carbamylcholine chloride and 200 ng of galanin ($n = 7$; coinjection group) or 200 ng of galanin ($n = 7$; galanin group).

CBF measurement: CBF was measured in cortical and subcortical regions with the [^{14}C]iodoantipyrine (IAP) method[14] by the tissue sampling technique at the end of the microinjection period (165 min after the injection of urethane and α-chloralose and more than 2 h after cannula insertion). A solution of [^{14}C]IAP (0.111 MBq dissolved in 0.7 ml of 0.9% sodium chloride) was infused i.v. for 45 s at a constant rate of 15 μl s^{-1} (Harvard Apparatus, Model 11). During the infusion of [^{14}C]IAP, arterial blood was sampled every 3–4 s in order to obtain the plasma concentration–time curve for the tracer. Approximately 45 s following the onset of the [^{14}C]IAP infusion, animals were subjected to euthanasia by a 1 ml bolus injection of thiopental followed by decapitation. The brains were removed rapidly and 24 regions were then dissected. The ^{14}C concentrations were measured by liquid scintillation spectrophotometer (Packard, TRI-CARB 2200) in solubilized tissue and plasma samples.

CBF calculations and statistics: CBF values (ml per 100 g min^{-1}; mean ± s.e.m.) were calculated from the tissue radioactivity and the time course of the plasma concentration of the tracer.[14] Comparisons between groups were analysed by one-way analysis of variance (ANOVA) followed by the Student–Newman–Keuls' multiple comparison test. Interhemispheric differences were determined by means of a paired Student *t*-test. The criterion for statistical significance was $p \leq 0.05$.

Results

Physiological parameters under the different conditions remained stable, although a significant (though meaningless) increase in pH_a ($p \leq 0.05$, ANOVA and Student–Newman–Keuls) was observed in the carbachol group when compared to the other groups.

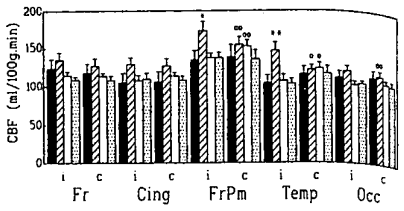

FIG. 1. Cerebral blood flow values (ml 100 g^{-1} min^{-1}, mean ± s.e.m.) in cortical regions after the microinjection (100 nl, 10 min) of 0.9% NaCl (■), 50 nmol carbachol (■), 50 nmol of carbachol and 200 ng of galanin (□) or 200 ng of galanin (□) into the substantia innominata. CBF was measured at the end of the microinjection period. Each column and vertical bar represents the mean ± s.e.m. i and c, ipsilateral and contralateral to the stimulation site. * and **, significantly different from the three other groups (ANOVA and Student–Newman–Keuls, $p \leq 0.05$ and $p \leq 0.02$, respectively). ^{a} and ^{aa}, significant interhemispheric asymmetry (paired Student *t*-test, $p \leq 0.05$ and $p \leq 0.01$, respectively). Fr, anterior frontal cortex; Cing, cingulate cortex; FrPm, frontoparietal motor cortex; Temp, temporal cortex; Occ, occipital cortex.

Microinjection of carbachol in the SI induced significant increases in CBF in two ipsilateral cortical areas, namely, the temporal (+41%, $p \leq 0.02$) and frontoparietal motor (+28%, $p \leq 0.05$) cortices compared with the other groups (Fig. 1). Following injection of carbachol, significant interhemispheric differences, corresponding to an increase in the ipsilateral side, were also noted in frontoparietal motor (+12%, $p \leq 0.01$), temporal (+20%, $p \leq 0.05$) and occipital cortices (+4%, $p \leq 0.01$) as well as in the inferior colliculi (+11%, $p \leq 0.01$) (Figs 1 and 2).

Coinjection of carbachol and galanin failed to modify CBF in the various cerebral regions compared with the sham group (Figs 1 and 2). In this situation, the vasodilatatory responses noted in the ipsilateral temporal and frontoparietal motor cortices after carbachol microinjection were significantly reduced (−37% and −25% respectively) compared with carbachol-stimulated rats (Fig. 1). Moreover, following coinjection, significant interhemispheric differences, corresponding to an increase in the contralateral site, were noted in the temporal (+16%, $p \leq 0.05$) and frontoparietal motor (+11%, $p \leq 0.01$) cortices as well as in the caudate-putamen (+19%, $p \leq 0.01$) (Figs 1 and 2).

The microinjection of galanin by itself did not affect CBF in any brain region investigated (Figs 1 and 2).

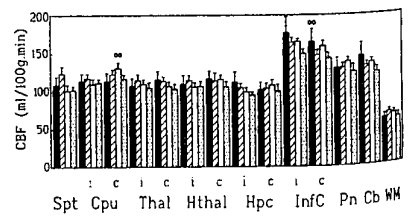

FIG. 2. Cerebral blood flow values (ml 100 g^{-1} min^{-1}, mean ± s.e.m.) in subcortical regions after the microinjection (100 nl, 10 min) of 0.9% NaCl (■), 50 nmol carbachol (■), 50 nmol of carbachol and 200 ng of galanin (□) or 200 ng of galanin (□) into the substantia innominata. CBF was measured at the end of the microinjection period. Each column and vertical bar represents the mean ± s.e.m. i and c, ipsilateral and contralateral to the stimulation site. **, significant interhemispheric asymmetry (paired Student *t*-test, $p \leq 0.01$). Spt, septum; Cpu, caudate-putamen; Thal, thalamus; Hthal, hypothalamus; Hpc, hippocampus; InfC, inferior colliculus; Pn, pons; Cb, cerebellum; WM, white matter (corpus callosum).

Discussion

The existence of a galaninergic innervation of rat cerebral arteries[15] would suggest the possible involvement of a potential influence of galanin on CBF. However, the lack of a direct vasomotor effect of this peptide[15] could imply that galanin may influence CBF via another transmitter system, possibly the cholinergic system. If so, one might suppose that galanin may modulate, in various neuroanatomical sites, the basalocortical cholinergic system, the vasodilatatory potential of which is well described.[1,2,3,5] First, this modulation could take place within the SI by an interaction between galaninergic neurones or axonal endings located in this structure and SI cholinergic neurones which are, in turn, directly or indirectly related with intraparenchymal microvessels. Secondly, the influence of galanin on CBF may also be exerted on the cerebral blood vessels since these vessels receive both a cholinergic[16] and a galaninergic[15] innervation. This vasomotor innervation, associated with the demonstration of cerebrovascular M_1 and M_3 muscarinic receptors and the activation of which is associated to the phosphoinositide turnover,[17] leaves open the possibility of an interaction between cholinergic and galaninergic second messengers systems as already demonstrated in the septo-hippocampal pathway.[10] Finally, since galaninergic neurones and receptors have been described in the neocortex,[18,19] one can also hypothesize that galanin may interact with cortical cholinergic interneurones, given the close relationship with these interneurones and intraparenchymal microvessels.[20,21]

In the present study, we have tested the possibility of such an interaction at the level of the SI. Coinjection of carbachol and galanin in the rat SI resulted in a remarkable inhibition of the carbachol-induced vasodilatation observed in the frontoparietal motor and temporal cortices. The fact that microinjections of galanin failed to modify CBF demonstrates that galanin possesses no intrinsic effects but exerts a modulatory inhibitory action on the vasodilatatory basalocortical cholinergic system. These results, which illustrate the inhibitory modulation of galanin on the cholinergic system, are in accordance with previous biochemical and functional studies in other experimental models. As an illustration, Fisone *et al*[9] have demonstrated that galanin induces a decrease in potassium-induced acetylcholine (ACh) release. In this respect, one could postulate that the inhibitory effect of galanin on the vasodilatatory basalocortical cholinergic system demonstrated here may be related to an inhibition of the cortical ACh release that is observed after SI stimulation[22] and assumed to be responsible for the vasodilatatory effect of SI activation. Moreover, it is possible that galanin acts post-synaptically on the SI cholinergic system by an interaction with the transduction mechanisms; such an effect has been described previously by Palazzi *et al*[10] in the hippocampus.

The present study demonstrates for the first time that galanin may be functionally involved in the SI. An important pathophysiological implication of this galaninergic modulation of the basalocortical cholinergic system, and its functional consequences, could correspond to neurodegenerative diseases such as Alzheimer's dementia. Indeed, in such pathologies, a hyper-innervation of the vestigial NBM cholinergic neurones by local galaninergic cells has been reported.[23] In addition, galanin and ACh coexist in some neurones of the SI/NBM.[12] Since the surviving cholinergic neurones may compensate for the well described loss of NBM cholinergic cell bodies by an increase in their firing rate[24] and, since neuropeptides are often released at higher frequences of neuronal excitation than are classical neurotransmitters, one might suppose that the cholinergic neurones of the NBM are over-inhibited by galanin, the release of which is greatly increased. On this basis, it could be that the memory impairment associated with Alzheimer's disease is the consequence, at least in part, not only, of cholinergic hypofunction but also galaninergic hyperfunction. Indeed, recent studies suggest that galanin might play an inhibitory role in learning and memory processes via an inhibitory modulation of cholinergic transmission. Mastropaolo *et al*[11] have demonstrated that galanin, injected into the ventral hippocampus, inhibits the ACh-induced improvement of performance of rats with basal forebrain lesions in a T-maze delayed alternation task. An implication of endogenous galanin in these cognitive functions has also been demonstrated through the use of galaninergic antagonists which, when injected intracerebroventricularly, improve the ability of rats in swim maze tasks.[25] Accordingly, such an inhibitory action of galanin in central cholinergic functions might be particularly deleterious in Alzheimer's disease.

Conclusion

The present results demonstrate for the first time that galanin exerts an inhibitory modulatory action on the vasodilatatory basalocortical cholinergic system, an effect mediated at least partly within the SI, and may thus possibly influence CBF indirectly.

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Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression

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CONVERGING evidence points to hypofunction of the left prefrontal cortex in depression. Repetitive transcranial magnetic stimulation (rTMS) activates neurons near the surface of the brain. We questioned whether daily left prefrontal rTMS might improve mood in depressed subjects and report a pilot study of such treatment in six highly medication-resistant depressed inpatients. Depression scores significantly improved for the group as a whole (Hamilton Depression Scores decreased from 23.8 ± 4.2 (s.d.) at baseline to 17.5 ± 8.4 after treatment; t = 3.03, 5DF, p = 0.02, two-tailed paired t-test). Two subjects showed robust mood improvement which occurred progressively over the course of several weeks. In one subject, depression symptoms completely remitted for the first time in 3 years. Daily left prefrontal rTMS appears to be safe, well tolerated and may alleviate depression.

Key words: Depression; transcranial magnetic stimulation; Prefrontal cortex; Treatments; Affective disorders

Introduction

Several lines of evidence indicate that the left prefrontal cortex is dysfunctional in depression.[1] Most functional neuroimaging studies of depressed subjects have found decreased left prefrontal activity, often in proportion to the rated severity of depression. Additionally, some studies have found that patients with left prefrontal strokes have an increased risk of developing depression. Finally, left unilateral electroconvulsive therapy (ECT) is more effective than right. Recently the technology of transcranial magnetic stimulation (TMS) has been developed and refined, providing the ability to stimulate superficial neurons of the cerebral cortex safely and subconvulsively. The ability to repeat quickly the magnetic stimulus (repetitive TMS; rTMS), has opened up yet another dimension of cortical activation and inhibition. In motor cortex, rTMS has different properties and neurobiological effects to those of single pulse TMS, perhaps because of the ability to stimulate during a neuron's refractory period.[2] Initially used to study motor function, rTMS has now been used to explore other brain functions[3] as well as to improve the slowed movement of Parkinson's disease temporarily when applied over the motor cortex.[4]

There has been recent interest in whether rTMS might have antidepressant actions if applied to the proper regions and with the appropriate dosing and frequency parameters.[5] Work in animal models of depression has demonstrated that TMS applied to the whole cortex has an antidepressant effect.[6] In humans, there have been two case reports of single pulse TMS (not repetitive) applied through circular coils centered over the vertex, with possible antidepressant action.[7,8] We hypothesized that the most effective antidepressant action of magnetic stimulation might be obtained by applying it frequently and repetitively (rTMS) to the left prefrontal cortex.

Subjects and Methods

We administered rTMS each morning for at least one week (5 days) to the left prefrontal cortex of six medication-resistant subjects, (mean age 46.5 years)